Claims 1-4 were rejected under 35 U.S.C. 112, first paragraph, for alleged lack of enablement.

The Examiner alleged that the term "warm blood animals" is too broad. The Examiner further stated that

> "There are no in vivo experiments or clinical applications of the compound toward an animal infected with a retrovirus, therefore, basis for the claimed technology is not sufficiently supported".

It is noted that Example 2 on pages 12-13 of the application concerns stimulated human peripheral blood mononuclear cells infected with HIV in the presence of 3-deoxythymidin-2'-ene. This example should be more than sufficient to satisfy the enablement requirement of 35 U.S.C. 112, first paragraph.

The Examiner's attention is directed to two recent Board Decisions, namely Ex parte Chwang, 231 U.S.P.Q. 751 (Bd. App. & Int. 1986) (which cited Cross v. Iizuka, 224 U.S.P.Q. 739 (Fed. Cir. 1985)) and Ex parte Krepelka et al, 231 U.S.P.Q. 746.

The Examiner is apparently trying to limit applicants only to their working examples and this is improper.

See In re Anderson, 176 USPQ 331, 333 (CCPA 1973), where the Court held that

> " we do not regard §112, first paragraph, as requiring a specific example of everying within the scope of a broad claim...What the Patent Office is here apparently attempting is to limit all claims to the specific examples, notwithstanding the disclosure of a broader invention. This it may not do."

" It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name ever such species. It is sufficient if the disclusre teaches those skilled in the art what the invention is and how to practice it."

Indeed, examples per se are not required to satisfy the requirements of 35 U.S.C. 112, first paragraph. See In re Strahilevitz, 212 USPQ 561, 562-563 (CCPA 1982); In re Stephens, 188 USPQ 659, 660-662 (CCPA 1976); In re Borkowski, 57 CCPA 946, 164 USPQ 642, 645-646 (CCPA 1970); In re Gay, 50 CCPA 725, 135 USPQ 311, 316 (CCPA 1962).

The Court held in In re Robins, 166 USPQ 552, 555-556 (CCPA 1970) that working examples are only one means of satisfying the enablement requirement of 35 U.S.C. 112, and that the mere listing of specific compounds, chemical substituents, solvents, cross-linking agents, etc. in the specification would in most cases provide suitable evidence of enablement equivalent to specific working examples utilizing each of the various components.

The disclosure as set forth by the applicants in the application must be given the presumption of correctness and operativeness by the Patent and Trademark Office. The only relevant concern of the Patent and Trademark Office is the truth of the assertions in the application. In any event, the burden is on the Patent and Trademark Office whenever a rejection is made for lack of enablement under Section 112. The Examiner must explain why the Examiner doubts the truth or accuracy of the statements in a

supporting disclosure to which the Examiner objects. The Examiner must back up such assertions with acceptable evidence or reasoning which contradicts applicants' contentions. See, for example, In re Marzoocchi, 169 USPQ 367, 369-370 (CCPA 1967) and In re Bowen, 181 USPQ 48, 50-52 (CCPA 1974).

The Examiner in the case at hand has not carried the Examiner's burden of showing the applicants' specification to be untrue or inaccurate; indeed, the Examiner gave no evidence or reasoning for the rejection.

Applicants do not believe that any experimentation would be necessary for one skilled in the art to practice their described invention. Assuming arguendo that a certain, limited degree of experimentation would be required for one skilled in that art to reproduce applicants' invention, such experimentation would not deter from applicants' satisfaction of the enablement requirement under 35 U.S.C. 112. See, for example, In re Miller, 169 USPQ 597, 602 (CCPA 1971); In re Angstadt, 190 USPQ 214, 218-219 (CCPA 1976); Ansul Company v Uniroyal, Inc., 179 USPQ 759, 763 (2d Cir. 1971), cert. denied, 172 USPQ 257 (1972); and Caldwell v. The United States, 175 USPQ 44, 47-48 (U.S. Ct. Cls. 1972).

It should be further noted that only those skilled in the art must be enabled, not the general public. In re Storrs, 114 USPQ 293, 296-297 (CCPA 1957).

Based on the above, applicants respectfully solicit withdrawal of the rejection of claims under 35 U.S.C. 112, first paragraph.

Claims 5 and 9 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Japanese 2,027,782 (Reference L).

In view of the present claims, all of which being directed to a method of treatment, withdrawal of this rejection is earnestly solicited.

Claims 1-10 were rejected under 35 U.S.C. 103 as being unpatentable over U.S.P. 3,817,982 to Verheyden et al (Reference A) in view of Japanese 2,027,782.

The English language abstract of Japanese 2,027,782 refers to the compounds therein as intermediates for the preparation of antibiotics, not as antivirals.

The Examiner acknowledged that "Applicants' 3-deoxythymidin-2'-ene differs [from Verheyden et al] in that it is a 5-methyl homolog of 2',3'-unsaturated uridine nucleoside".

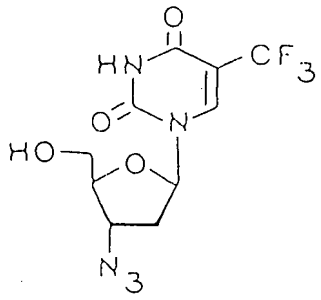
The abstract of Verheyden et al mentions the production of 2',3'-unsaturated nucleosides as antivirals, but does not mention retrovirus, let alone HTLV-III/LAV (HIV-I). The antiviral agents that are presently in clinical use or shown to be effective against a variety of DNA and RNA viruses are not useful against HIV-I. Therefore, it is not obvious that a compound which is active against RNA and DNA viruses will be clinically useful against the AIDS-virus.

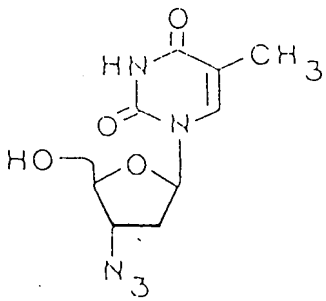
For example, ribavirin, which has very broad spectrum of antiviral activity against RNA and DNA viruses, when given to patients with AIDS in a controlled experiment resulted in more patient deaths than produced by the control-placebo.

The claims 1-29 of Verheyden et al refer only to improved methods of preparation of compounds. There is no recitation for any biological activity in any of the claims. In view of the above, the Verheyden et al reference is deemed to be non-enabling with respect to treatment of retroviruses.

When Verheyden et al filed their application on December 29, 1971 that ultimately matured into their patent, there were no reported cases of AIDS (see applicants' claim 3).

Verheyden et al describe a compound which is close in structure to AZT, a compound presently used in a treatment of AIDS.



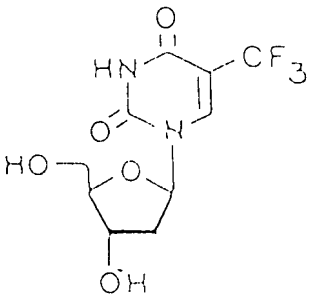




the Verheyden et al compound AZT

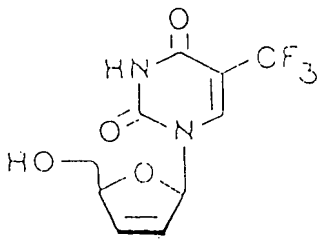
Whereas AZT is a potent antiviral against HIV-I, the Verheyden et al compound, has absolutely no activity against this virus at a concentration of more than 100 uM. AZT has an $EC_{50}$ of 0.002 uM. See page 16 and Figure 1 of the enclosed copy of Lin et al, "Synthesis and Antiviral Activity of Various 3'-Azido Analogues of Pyrimidine Deoxyribonucleosides Against Human Immunodeficiency Virus (HIV-I, HTLV-III/LAV)".

Therefore, replacement of $-CH_3$ of AZT with $-CF_3$ produced an inert compound, but this was not obvious.

The reference cited in column 13, second paragraph indicates antiviral activity of 2',3'-dideoxy-2',3'-unsaturated trifluoromenthyluridine against the vaccinia virus, not HIV-I. As indicated above, one can not assume anti-HIV-I activity merely because it has activity with a different virus. Of relevance is the enclosed copy of Khwaja, T.A. and Heidelberg, C., J. Med. chem., 12, 543 (1966) which indicates that the unsaturated trifluoromethyluridine analog was 1/1000 as active as the saturated analog, 5-trifluoromethyl-2'-deoxyuridine.



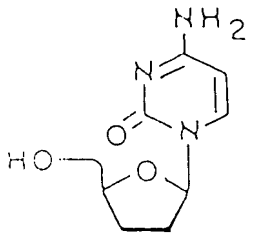
Saturated

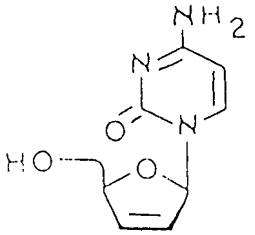


Unsaturated

Again it is therefore not obvious that the 2',3'-unsaturated analog of thymidine (compound as used in the present invention) would be markedly more active than the 2',3'-saturated analog of thymidine. Therefore, just the reverse, of what one would have predicted to be obvious, was observed.

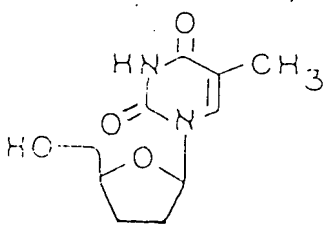
Another example of where modification of structure does not result in an obvious result is seen in a comparison of 2',3'-dideoxycytidine with 2',3'-dideoxy-2',3'-didehydrocytidine:

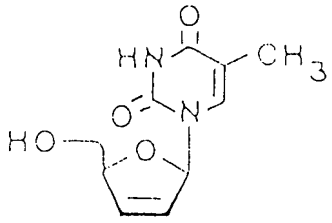




These two compounds have similar activity with $EC_{50}$ for the saturated compound being 0.011 $\mu$M, and that for the unsaturated analog having an $EC_{50}$ of 0.005 $\mu$M. Also see page 313 of Lin et al "Antiviral Activity of 2',3'-Dideoxycytidin-2'-ene (2',3'-dideoxy-2',3'-didehydrocytidine) Against Human Immunodeficiency Virus <u>In Vitro</u>", <u>Biochemical Pharmacology</u>, Vol. 31, No. 3, pp. 311-316, (1987). The difference being very slight.

However, comparison of the corresponding thymidine analogs 3'-deoxythymidine with the compound used in the present invention, 3'-deoxythymidin-2'-ene,





revealed a finding that could not have been predicted based on a comparison of the corresponding cytidine analogs. 3'-Deoxythymidine has an $EC_{50}$ of 0.170 $\mu$M, whereas the compound used in the present invention, 3'-deoxythymidine-2-'ene, has an $EC_{50}$ of 0.009 $\mu$M. See page

4 of the enclosed copy of Lin et al, "Potent and Selective In vitro Activity of 3'-Deoxythymidin-2'-ene (3'-Deoxy-2',3'-Didehydrothymidine) Against Human Immunodeficiencey Virus".

Hence, the difference in antiviral activity against HIV-I of the saturated and unsaturated cytidine analogs differed by an insignificant factor of 2, whereas the unsaturated analog of thymidine is about 19-times more potent than the saturated analog. It was not obvious that such a marked increase in activity would have been observed based on what was found with the corresponding cytidine analogs.

The following papers, copies of which are enclosed, indicate variation in activity among different viruses:

(1) De Clercq , Journal of Antimicrobial Chemotherapy, 14, Suppl. A, 85-95 (1984) -see Table II on page 88

(2) Biochemical Pharmacology, Vol. 29, pp. 1849-1851

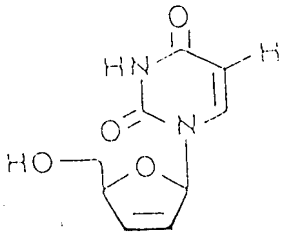
(3) Machida, Antimicrobial Agents and Chemotherapy, Vol. 29, No. 3, 524-526, Mar. 1986

(4) De Clercq et al, J. Med. Chem., 29, 213-217, (1986) - see Table II on page 214.

The Examiner alleged that Verheyden et al teach the equivalents of 5-lower alkyl of 2',3'-unsaturated cytidin-2'-ene nucleosides. However, it is reported in Kim et al., J. Med. Chem., 30, 862, (1987), a copy of which is enclosed, that whereas 2',3'-dideoxycytidine is very active

against HIV-I, the insertion of a $-CH_3$ moiety in the 5-position abolished its antiviral activity against HIV-I and had increased cytotoxicity.

Furthermore, removal of the $-CH_3$ moiety of the subject compound results in the formation of 2',3'-dideoxy-2',3'-didehydrouridine, a compound which has no activity against HIV-I (Herdewijn et al., J. Med. Chem., 30, 1273, (1987), a copy of which is enclosed). Thus again, slight modifications of structure do not necessarily result in "obvious" results.



In view of the above, withdrawal of the rejection or claims under 35 U.S.C. 103 is earnestly requested.

The non-applied art is not believed to be as relevant as the art discussed above.

Applicants believe that this application is now in condition for allowance of all claims therein, and the early issuance of a Notice of Allowance is respectfully requested.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 on OCTOBER 6, 1987

Sprung Horn Kramer & Woods

By _____

Date OCTOBER 6, 1987